A Phase II Study of Pemetrexed in Patients with Recurrent Thymoma and Thymic Carcinoma.

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Abstract:

Background: Thymoma and thymic carcinoma are neoplastic diseases with reported chemosensitivity to a broad range of agents. However, due to the rarity of these diseases, few prospective trials have been conducted in patients with advanced thymic malignancies. We conducted a prospective phase II trial to evaluate the clinical activity of pemetrexed, a multi-targeted anti-folate agent, in previously treated patients with thymoma (THY) and thymic carcinoma (TC). **Patients and Methods**: Twenty-seven previously treated patients (THY = 16, TC = 11) with advanced, unresectable disease were treated with pemetrexed 500 mg/m^2 IV every three weeks for a maximum of 6 cycles or until undue toxicity or progressive disease. All patients received folic acid, vitamin B12 and steroid prophylaxis. **Results**: The median number of cycles administered was 6 (range 1-6). Nine patients with a total of 14 events had grade 3 toxicities; no grade 4 toxicities were noted. In 26 fully-evaluable patients, two complete and three partial responses (RECIST) were documented (all in patients with stage IVA THY, except one partial response with stage IVA TC). Fourteen patients completed the full 6 cycles of treatment, 7 patients progressed while on therapy, 5 patients discontinued therapy for intolerance, and 1 patient discontinued for progressive Morvan's Syndrome. The median progression free survival for all patients was 10.6 months (THY = 12.1 months vs. TC = 2.9 months). With 23 deaths at data cutoff, the median overall survival is 28.7 months (THY = 46.4 months vs. TC = 9.8 months). **Conclusions**: Pemetrexed is an active agent in this heavily pretreated population of patients with recurrent thymic malignancies, especially thymoma.

Key words: Thymoma, thymic cancer, thymic epithelial malignancies, Pemetrexed.

Introduction

Thymic malignancies are rare neoplasms, with a reported incidence of 0.15 cases per 100,000.[1] They are the most common tumors presenting in the anterior mediastinum and account for 50% of such neoplasms in adults.[2, 3] Thymic carcinoma represents a more malignant phenotype of thymic tumors, typically presenting with a more aggressive clinical course. Surgical resection remains the mainstay of treatment for patients with localized thymic malignancies, whereas radiation and systemic chemotherapy are employed for unresectable or metastatic disease. In patients with recurrent disease, additional chemotherapy is used for those deemed inoperable. Platinum-based regimens have demonstrated significant response rates and improved survival for such patients, but in relapsed disease, no established standard of care exists.

Multiple chemotherapy drugs are active in thymic malignancies, and the relatively indolent nature of this disease makes it a good candidate for exploring single agent activity of new therapies in the relapse setting. Pemetrexed (Alimta, Eli Lilly & Co., Indianapolis, IN) is a multi-targeted antifolate agent with demonstrated activity in a variety of malignancies.[4] Importantly, pemetrexed has significant activity alone, or in combination, in patients with other intra-thoracic tumors, including malignant mesothelioma and non-small cell lung cancer.[5-8] At the time this trial was conceptualized, it was clinically rational to investigate pemetrexed in patients with relapsed thymic malignancies. We therefore conducted a Phase II trial (ClinicalTrials.gov identifier: NCT00198133) to evaluate the clinical activity of pemetrexed in patients with recurrent or metastatic thymoma and thymic carcinoma who relapsed after systemic therapy. We present survival outcomes of patients enrolled in this trial.

PATIENTS AND METHODS

Patients with histologically confirmed invasive, surgically incurable, metastatic/advanced thymoma (THY) or thymic carcinoma (TC) that had progressed after initial systemic chemotherapy were eligible for this study. Original biopsy of the tumor was deemed sufficient for diagnosis and inclusion on trial, and patients were not stratified by histology, although eligible patients were required to have measurable disease on standard radiologic imaging obtained within six weeks prior to registration on study. There was no limit to the number of prior treatments. Further eligibility criteria included adequate hepatic function (serum bilirubin $\leq$ 1.5mg/dl), renal function (calculated creatinine clearance of $\geq$ 45ml/min by Cockcroft/Gault method), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 prior to entry. Hematologic requirements were granulocytes $\geq$ 1500/mm^3 and platelets $\geq$ 100,000/mm^3. Patients were at least 18 years of age at the time of entry or allowed in with consent of their parent or legal guardian. Patients receiving a stable dose of corticosteroid for the treatment of myasthenia gravis were permitted on trial while those with acute intercurrent complications, such as infection or inadequate post-surgical wound healing were deemed ineligible.

Patients with known hypersensitivity to pemetrexed or any component of the product were not eligible for study. Due to its potential teratogenicity, patients who were pregnant or nursing were excluded from study. For similar reasons, patients of reproductive age and capacity were permitted on study with their commitment to adhere to strict contraceptive practices while receiving pemetrexed on trial. Treatment with other non-approved or investigational agents within 30 days prior to enrollment disqualified a patient from this study. The presence of clinically relevant third-space fluid collections not amenable to drainage (including but not limited to ascites or pleural effusions) and inability to interrupt aspirin or other non-steroidal anti-inflammatory drugs for a 5-day period also excluded patients from study. All patients were provided full study description and information and required to sign a written informed consent form

prior to the initiation of treatment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Treatment Procedures

All eligible patients were treated with pemetrexed 500 mg/m^2 as a 10-minute intravenous infusion once every 21 days, for a pre-planned maximum of 6 cycles, disease progression or undue toxicity, whichever occurred first. All patients were pretreated with vitamin B12, 1000 mcg, given as intramuscular injection 1-2 weeks prior to the first dose of pemetrexed and repeated approximately every 9 weeks until 3 weeks after the last treatment dose. Similarly, all patients received folic acid supplementation (350-1000 mcg) given orally beginning 5-7 days prior to initial dose of pemetrexed and continued until 3 weeks following the last dose of chemotherapy. Dexamethasone (4 mg oral or equivalent) was administered twice daily on the day prior to pemetrexed, day of treatment, and the day following chemotherapy.

Pemetrexed-related toxicities were managed with either temporary dose delays or subsequent dose reductions where appropriate. Dose delays >14 days prompted removal of patient from study protocol. Dose reductions of pemetrexed by 25% were implemented for grade 3 and 4 hematopoietic toxicities (after delaying treatment until adequate recovery of granulocytes $\geq$ 1500/mm^3 and platelets $\geq$ 100,000/mm^3). If greater than two dose reductions (25% then 50%) for hematopoietic toxicity were required, patients were removed from study. A similar approach was used in the management of non-hematopoietic toxicities.

Efficacy and Safety

Patients were evaluated clinically, and with laboratory assessments with every cycle of pemetrexed (every three weeks) to determine their tolerance and eligibility for subsequent drug administration. Baseline, followed by repeat imaging with computerized tomography (CT) scans was obtained every six weeks (2 cycles) to evaluate response to treatment.

Tumor response and progression were defined using the Response Evaluation Criteria in Solid Tumors (RECIST).[10] Duration of overall response is defined as the time from when measurement criteria are first met to achieve CR or PR (whichever is recorded first) until the first date that recurrent or progressive disease is objectively documented. Duration of stable disease is similarly defined as the date treatment started to the date of objective disease progression. The first evaluation for response assessment was within 6 weeks of first cycle of treatment. The final objective response rate (ORR) was determined by calculating the total number of patients that fulfilled criteria to achieve a CR or PR divided by the total number of patients treated on study. All patients evaluable for toxicity or response were included in the denominator for this calculation.

Adverse events (AE) were recorded and graded based on the National Cancer Institute Common Terminology Criteria Version 2.0 at each study visit.

Outcomes

The primary endpoint of this study was the objective response rate (complete and partial). Secondary endpoints included progression free survival (PFS), defined as the time from the initiation of treatment until disease progression or death, duration of response, defined as the time from onset of response to onset of progression, and drug-specific toxicity.

Statistical Analysis

The study was designed to test whether the ORR of pemetrexed is > 20% (alternative hypothesis $p = 0.2$) versus an objective response of <5% (null hypothesis $p = 0.05$). Target accrual for this study was 27 patients, utilizing a two-stage design that would prematurely close the study after 18 patients were enrolled if no evidence of response was detected in the first cohort. If one or more responses were identified among the first group, the study was to proceed with enrollment of 9 additional patients. If at least four objective responses were observed, this would be considered sufficient evidence that the true objective response rate is at least 20%. The determination of the sample size conformed to the requirement that the maximum number of patients treated be minimized, while ensuring a probability of early study termination of <2%, if the true objective response rate was higher than 20%. The study was designed to generate power greater than 80% if the true response rate was at least 20% at a significance (alpha) level of 5%. At the completion of the study, two-sided 95% confidence intervals of the true response rate were produced by the method of Atkinson and Brown[11]. These confidence intervals take into consideration the sequential design of the study and are, as a rule, slightly wider than the usual confidence intervals used in single-stage designs. For confidence intervals of responses within cancer-type sub-group, routine confidence intervals based on the exact binomial distribution were constructed.

Progression-free survival and duration of response were calculated by the Kaplan-Meier method. Calculation of 95% confidence intervals for medians were derived using the Brookmeyer-Crowley method. All analyses were carried out by SAS version 9.3 (The SAS Institute, Cary, NC).

RESULTS

Patients

Twenty-seven patients with advanced thymoma or thymic carcinoma were enrolled on trial from February 2005 to November 2005. Patient characteristics are listed in Table 1. The median age of patients enrolled on trial was 52 years. Gender was evenly balanced among patients (48% female and 52% male), and the majority of patients were Caucasian (85%). Sixteen of the 27 patients enrolled had thymoma (THY) while the remaining 11 patients had thymic carcinoma (TC). Performance status (PS) was < 2 for all patients enrolled (48% were PS = 0, and 52% were PS = 1). All the patients had received at least 1 line of chemotherapy prior to enrolment, with a median of 2 prior lines of therapy (1-5), and 74% had received prior radiotherapy. Prior chemotherapy was evenly split between cisplatin and carboplatin containing regimens (48% each). The most common sites of metastatic involvement were lung (59%), pleura (37%), and liver (22%).

Efficacy

Fourteen of the 27 patients enrolled completed the full course of 6 cycles of pemetrexed. One patient was not evaluable for response because he withdrew from the study before the first evaluation. Four objective responses (two CR, two PR) were observed among the 18 evaluable subjects accrued in the first stage and one additional response (PR) among the nine subjects enrolled in the second stage. Overall, there were two complete responses (7.4%) and 3 partial responses (11.1%), for an overall response rate (CR + PR) of 19.2% (95% CI taking into account the two-stage nature of the study 6.3-38.1). The majority of responses were seen in patients with thymoma, in which 4 of the 15 patients 26.7%, (95% CI 7.8 to 55.1) had an overall response, while only one response (PR) was demonstrated in the 11 patients with thymic carcinoma, 9.1% (95% CI 0.2-41.3). The median duration of response for the 4 THY patients who responded was 4 months (range 3.26 – 6.28 months) and the response lasted for 3.8 months in the 1 TC patient with a PR (Table 2).

Seven patients discontinued treatment due to disease progression during treatment (26%). Seventeen patients (65.4%) had a best response of stable disease (SD) while on study (Table 3). Overall, the median time to SD was 2.76 months (95% CI 1.18 – 6.09 months) and the median duration of SD was 4.9 months (95% CI 1.38- 8.72 months). Patients with THY had a longer SD duration of 6.09 months (95% CI 1.35-7.37 months) compared to 2.34 months (95% CI 1.38 -10.23, p= 0.7973) for TC patients.

The median time to progression for all patients was 10.6 months (95% CI 2.9-13.4months). The median progression-free survival in the two cancer types was 12.1 months in patients with thymoma (95% CI 6.3-14.5 months) versus 2.9 months for patients with thymic carcinoma (95% CI 0.6-15.0 months, p= 0.4156), Figure 1. With 23 deaths at the time of data cut-off in August 2015, the median overall survival is 28.7 months (95% CI 9.8-47.2 months). The median OS among patients with thymoma was 46.4 months (95% CI 11.3-67.5 months) versus 9.8 months in patients with thymic carcinoma (95% 3.4-32 months, *p*=0.0709) Figure 2. The progression-free and overall survival were not statistically different between the two groups. One patient with THY who had achieved a CR with pemetrexed remained alive at the time of data cutoff (Table 2). Prior to enrolling on study, she had received 2 lines of cisplatin-based combination therapy and a 3rd line of treatment with erlotinib.

Adverse Events

Treatment was generally well tolerated. Overall, the adverse events reported in this study are consistent with the known toxicity profile of pemetrexed. Nine patients (33%) reported grade-3 toxicities and no grade-4 toxicities occurred in the 27 patients enrolled on study. The most frequent grade-3 toxicities included infection (3 patients), cardiopulmonary events (3 patients) and gastrointestinal events (3 patients). Hematologic toxicity was mild, with only one grade-3 neutropenia reported. Similarly,

abnormalities in serum chemistry were infrequent and mild, with only one patient developing grade-2 hepatic transaminase elevations.

Discussion

In this heavily pretreated patient population, pemetrexed, a 2nd generation antifolate agent produced an objective response of 26% (4/15) in thymoma. Two complete responses and 2 partial responses were documented, whereas there was only one partial response in thymic carcinoma. The response rate of 9% in thymic carcinoma suggests that pemetrexed has minimal activity in this more aggressive phenotype. This is the first study to prospectively demonstrate the clinical activity of pemetrexed in thymic malignancies and solidifies the role of pemetrexed in the second line, and beyond in advanced thymoma. While this study was being carried out, a Phase I trial of pemetrexed in multiple solid malignancies conducted in Japan demonstrated a partial response in one of two included patients with thymoma.[9] In addition, a retrospective series of 16 patients with recurrent or metastatic thymic tumors, pemetrexed alone (*N*=14) or in combination (*N*=2) produced one partial response or stable disease (*N*=5) among 6 patients with THY and 1 partial response and stable disease (*N*=5) in 10 patients with TC. After a median follow up of 21.2 months for THY and 13.5 months for TC, the median PFS (13.8 vs 6.5 months) and OS (20.1 vs 12.7 months) were also more favorable for thymoma compared to thymic carcinoma.[12]

Among all 26 evaluable patients enrolled in this study, the overall response to a 3 weekly 500mg intravenous dose of pemetrexed was 19%. Although the trial was not set up to determine a difference in response between the 2 subtypes of thymic malignancies, there was a remarkable difference in response to pemetrexed in the THY cohort compared to the population with TC (26% vs 9%). Progression free survival was also higher with thymoma compared to thymic cancer (12.1 months vs 2.9 months). At the time of the initiation of the trial, it was common to lump both histologies under one category. Today,

there is growing evidence that these thymic malignancies represent histologically and molecularly distinct neoplasms. [13-15] Compared to thymoma, thymic carcinoma is more aggressive and is more likely to metastasize outside the chest cavity.[16] Genome analysis has revealed a preponderance of thymic carcinoma (and WHO Class B3 THY) in a subgroup of thymic malignancies characterized by chromosomal instability; particularly loss of 16q, and unfavorable survival outcomes.[17] In addition, CD117 (c-KIT) is frequently overexpressed in thymic carcinoma but not in thymoma.[18, 19] These biologic differences may explain the results of our study. Indeed, a Phase II study of the combination of paclitaxel and carboplatin in recurrent thymic malignancies demonstrated an ORR of 42.9% in patients with THY compared to 21.7% in the cohort with TC[20]. More recently, in a Phase II study of cixutumumab, an insulin growth factor receptor-1 monoclonal antibody (IGFR-1), investigators reported a 14% (5/37) partial response rate in thymoma whereas there was no CR/PR among the 12 patients with TC.[21] Conversely, a Phase II trial of sunitinib in thymic malignancies showed a response rate (PR) of 26% among patients with thymic carcinoma compared to 6% in Thymoma[22]. Survival numbers were not reported but based on this, sunitinib is recommended for patients with chemotherapy refractory thymic carcinoma rather than thymoma.[23]

Varied responses specifically to pemetrexed in different histologies of lung epithelial cancer is also recognized.[24, 25] Thymidylate synthase (TS), a key enzyme targeted by pemetrexed is over-expressed in squamous cell lung cancer and this may explain why pemetrexed is less active in this histologic type versus the adenocarcinoma variant of lung cancer.[26] On the other hand, retrospective studies have been inconsistent about the role of TS expression as a predictor of response to pemetrexed in mesothelioma.[27-29] A review of 56 cases of thymic malignancies revealed TS expression in 61% of tumors. Of note, significantly higher TS expression was observed in thymic carcinoma compared to thymoma, with higher TS expression correlated with

poorer survival.[30] The relationship between TS expression and response to pemetrexed has not been established in thymic malignancies and was not examined in this study.

In this trial, pemetrexed was well tolerated, with 14 of the 27 patients completing all 6 scheduled cycles of therapy. There were no Grade 4 events and the commonest Grade 1-2 events were fatigue (52%) and anorexia (37%) (Table 3). A major limitation of the study is the relatively small number of patients. This may account for the apparent lack of a statistically significant survival benefit with pemetrexed in thymoma compared to thymic carcinoma. We also did not investigate the expression of enzymes crucial for pemetrexed metabolism, so we are unable to comment on potential biomarkers of response to pemetrexed across the WHO classes of thymic malignancies captured in this trial. Another major shortcoming of the study was the pre-specification to treat for a maximum of 6 cycles of pemetrexed (4.5 months). Fourteen of the 27 enrolled patients (52%) completed these 6 cycles and it is conceivable that some of these may have tolerated, and possibly benefited from additional cycles of treatment. Indeed, the median duration of response among the THY patients with a PR/CR was 4 months which suggests that response continued beyond treatment. We also note that our study design required an evaluation of response to treatment within 6 weeks of starting therapy. Given the indolent nature of thymic malignancies, it could be argued that this is perhaps too short an interval particularly as the median time to SD in this study was 2.76 months.

Altogether, prospective clinical trials in patients with recurrent thymic malignancies are few, and most of these report response rates less than 20% (Table 4). A response rate of approximately 25% to pemetrexed in a heavily pretreated population of patients with recurrent thymoma therefore makes this agent one of the most active to date and undergirds its role as a 2nd line agent after platinum-based treatment in thymoma but not in thymic carcinoma. More work needs to be done to determine the role of single agent or combination regimens with pemetrexed in the first line.

Key Message

Thymic malignancies are rare, with no established standard chemotherapy for recurrent disease. Pemetrexed is active as a second line agent for recurrent thymoma but information on survival outcomes is lacking. In this single arm Phase II study, pemetrexed was associated with an overall response rate of 26% in thymoma vs 9% in thymic carcinoma with median PFS of 12.1 vs 2.9 months and median OS of 46.4 vs 9.8 months respectively.

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A Phase II Study of Pemetrexed in Patients with Recurrent Thymoma and Thymic Carcinoma- Tables

Table 1. Baseline Characteristics

	Thymoma *N*= 16	Thymic carcinoma *N*= 11	Total *N*= 27
Median age, years (range)	51.5 (28-83)	52 (26-80)	52 (26-83)
Gender			
Female	9 (56%)	4 (36%)	13 (48%)
Male	7 (44%)	7 (64%)	14 (52%)
Race			
Asian	1 (6%)	1 (9%)	2 (7%)
Black	2 (13%)	0	2 (7%)
White	13 (81%)	10 (91%)	23 (85%)
ECOG PS			
0	8 (50%)	5 (45%)	13 (48%)
1	8 (50%)	6 (55%)	14 (52%)
Prior Chemotherapy* (range)	2 (1-5)	2 (1-4)	2 (1-5)
Tumor Stage			
IVA	13 (81%)	5 (45%)	17 (63%)
IVB	3 (19%)	6 (55%)	10 (37%)
WHO Histology Subclass			
B1	1 (6%)		1 (4%)
B1/B2	2 (13%)		2 (7%)
B2	1 (6%)		1 (4%)
B2/B3	4 (25%)		4 (15%)
B3	8 (50%)		8 (30%)
Thymic Carcinoma		11(100%)	11 (41%)
Autoimmune Disease			
Myasthenia Gravis	2 (13%)	0	2 (7%)
Other	3 (19%)	0	3 (11%)
Site of Metastatic Disease			
Locally Advanced			15 (56%)
Pleura	14	8	10 (37%)
Lung	3	3	16 (59%)
Liver	0	2	4 (15%)
Brain	2	0	2 (7%)

Data presented as number of patients (%) unless otherwise stated
*Median number of prior chemotherapy regimens
ECOG PS, Eastern Cooperative Oncology Group Performance Status

Table 2. Characteristics of patients who responded to pemetrexed

Patient ID	Gender	Histology	Previous treatment(s)	*Response to previous treatment(s)	Site of relapse	Best response to pemetrexed	Duration of response to pemetrexed (months)	PFS/OS (months)
5	M	B2 THY	PAC, Cis/Etoposide Gemcitabine	NA	NA	PR	3.3	10/17
7	M	B2/B3 THY	Carbo/Paclitaxel	CR	Pleura	CR	3.4	11/86
#11	F	B3 THY	PAC, Cis/Etoposide, Erlotinib	PR	Pleura, Lung	CR	6.3	15/102
18	F	B3 THY	PAC, Carbo/Paclitaxel, 5 FU/LVN Bev/Erlotinib	PR	NA	PR	4.5	11/68
27	F	TC	Cis/Etoposide	NA	Pleura, Mediastinum	PR	3.8	10/32

M = Male, F = Female, THY = Thymoma, TC = Thymic Carcinoma, NA = Not Available, PFS = Progression Free Survival, OS = Overall Survival, PAC = Cisplatin, Adriamycin, Cyclophosphamide, Cis = Cisplatin, Carbo = Carboplatin, 5FU/LN = 5-Fluoruracil and Leucovorin, Bev = Bevacizumab, PR = Partial Response, CR = Complete Response
*best response to any systemic therapy prior to study.
#This patient was alive as of data cutoff

Table 3. Response to pemetrexed in patients with Thymoma and Thymic Carcinoma

Best overall Response	Thymoma *N*= 16 (%)	Thymic carcinoma *N*= 11 (%)	Total *N*= 27 (%)
Complete response	2 (13)	0	2 (7)
Partial response	2 (13)	1 (9)	3 (11)
Stable disease	12 (74)	10 (91)	22 (82)
Overall response rate*	4 (25)	1 (9)	5 (19)

*Overall response rate is a composite of complete response and partial response. N is number of patients. Best overall response according to RECIST v1.1

Table 4. Summary of TRAEs* with Pemetrexed (*N*=27)

	No. (%)		
TRAE	Grade 1-2	Grade 3	Grade 4
Fatigue	14 (52)	0	0
Anorexia	10 (37)	0	0
Dyspnea	9 (33)	1 (4)	0
Cough	8 (30)	0	0
Nausea	7 (26)	0	0
Constipation	5 (19)	1 (4)	0
Diarrhea	5 (19)	0	0
Fever	5 (19)	0	0
Pruritus/itching	5 (19)	0	0
Rash	5 (19)	0	0
Vomiting	5 (19)	0	0
Insomnia	4 (15)	0	0
Intermittent nausea	4 (15)	0	0
Mucositis	4 (15)	0	0
Dyspepsia	3 (11)	0	0
Sinus Drainage	3 (11)	0	0
Taste Alteration	3 (11)	0	0

TRAE were assessed during and for up to 30 days after the last dose of study treatment
Abbreviation: TRAE, Treatment-related adverse event
*Reported in more than 10% of patients

Table 5. Prospective systemic therapeutic trials in recurrent thymic malignancies

Author (Year)	Regimen	Number of patients(T/TC)	Responses (CR or PR)	Median Survival, years
Palmieri (2002)[31]	Octreotide/Lanreotide+/-Prednisone	10 (T) 3 (TC)	4 (T) 1 (TC)	NR
Loehrer (2004)[32]	Octreotide+/-Prednisone	32 (T) 6 (TC)	12 (all T)	NR
Kurup (2005)[33]	Gefitinib	19 (T) 7 (TC)	1 (T)	NR
Bedano (2008)[34]	Erlotinib + Bevacizumab	11 (T) 7 (TC)	0	NR
Salter (2008)[35]	Imatinib	11 (TC)	0	NR
Giaccone (2009)	Imatinib	2 (T) 5 (TC)	 0	0.33
Palmieri (2012)[36]	Imatinib	12 (T) 3 (TC)	0	NR
Giaccone (2011)[37]	Belinostat	25 (T) 16 (TC)	2 (both T)	1.6
Rajan (2014)[21]	Cixutumumab	37 (T) 12 (TC)	5 (all T)	2.3 (T) 0.7 (TC)
Inoue (2014)[38]	Carboplatin + Amrubicin	3 (T) 14 (TC)	3 (TC)	2.3
Gubens (2015)[39]	Saracatinib	12 (T) 9 (TC)	0	NR
Thomas (2015)[22]	Sunitinib	16 (T) 23 (TC)	1 (T) 6 (TC)	NR
Wakelee (2015)[40]	Amrubicin	14 (T) 19 (TC)	4 (T) 2 (TC)	NR
Zucali (2018)[41]	Everolimus	32 (T) 19 (TC)	3 (T) 3 (TC)	NR 1.2

Abbreviations; T= Thymoma, TC= Thymic Carcinoma, CR= Complete Response, PR= Partial response, NR= Not Reached

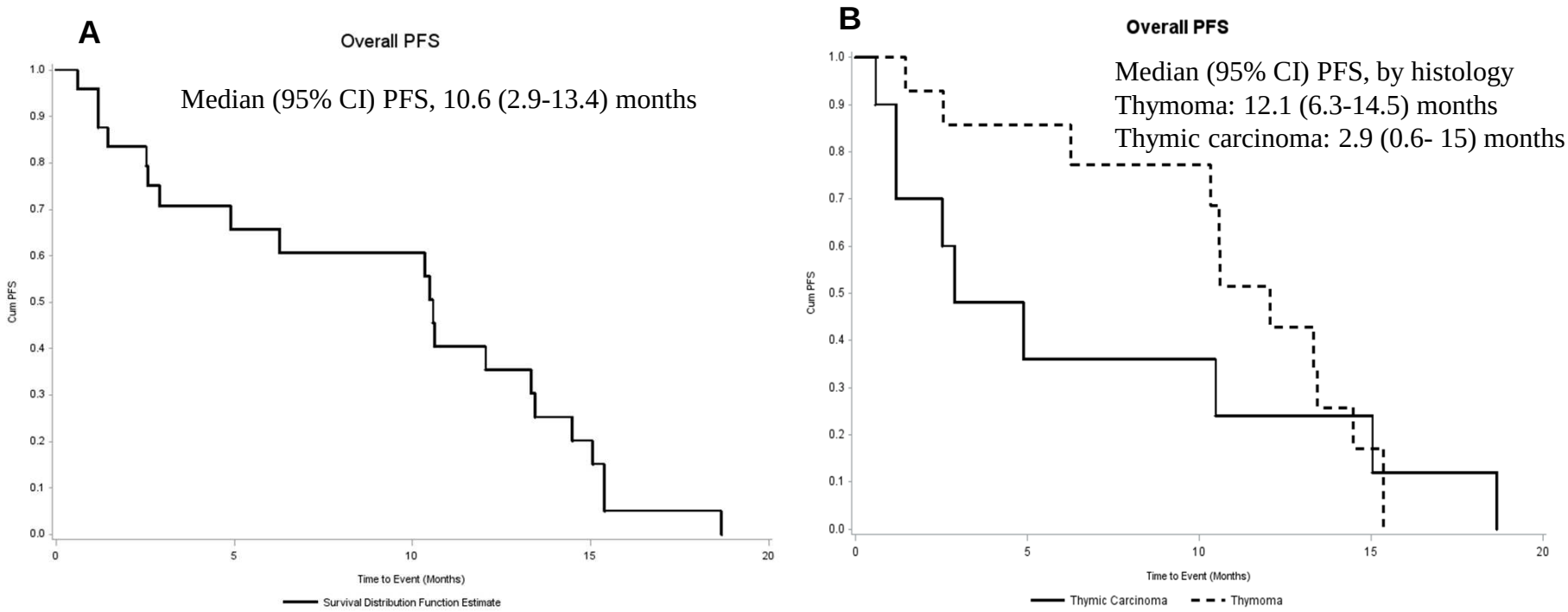

Figure 1: Progression free survival in patients with recurrent thymic malignancies treated with pemetrexed (A) Composite progression free survival for all patients (N=27). (B). Progression-free survival based on different histologies, Thymic carcinoma (N=11) and Thymoma (N=16)

Abbreviation: cum PFS= cumulative progression-free survival

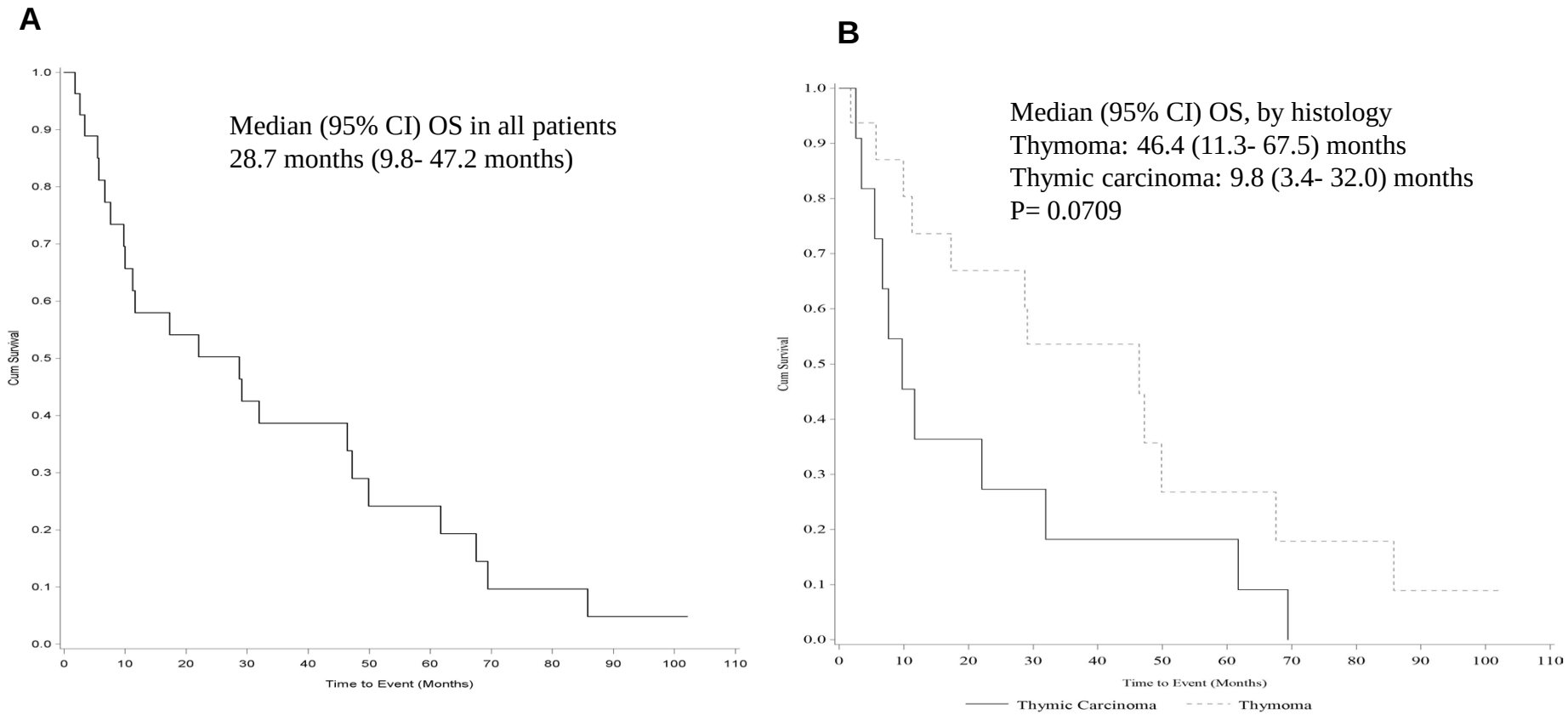

Figure 2: Overall Survival in patients with recurrent thymic malignancies treated with pemetrexed
(A) Composite overall survival for all patients (N=27). (B). Overall survival based on different histologies. Thymic carcinoma (N=11) and Thymoma (N=16)

Abbreviation: Cum survival= cumulative overall survival. OS= Overall survival